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Hormonal regulation of gastric emptying and its application in the therapy of gastroparesis

TL Peeters

TL Peeters, MD, Gut Hormone Lab, Leuven, Belgium

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The gastrointestinal system is the largest endocrine organ of the body. More than twenty different types of neuroendocrine cells secrete more than eighty peptides. Despite a prolific literature, the physiologic function and clinical relevance of most of these peptides remains to be identified or is poorly understood. Several of these peptides are able to affect gastrointestinal motor activity in general and gastric emptying in particular. For two of these peptides, motilin and cholecystokinin, the study of their role in the regulation of gastric emptying has led to the development of drugs which may find clinical application even though their physiological role remains uncertain. For this reason this paper will be limited to these two peptides.

Cholecystokinin (CCK) was first described over 60 years ago as a putative regula tor of gallbladder contraction and was shown in 1966 to be identical with pancreozymin, the agent postulated to be released by fats or proteins and causing pancreatic enzyme secretion. Originally isolated as a 33-amino acid peptide, many other molecular forms exist, all however sharing the amidated carb oxy terminal pentapeptide Gly-Trp-Asp-Met-Phe-NH2 which is also present in gastrin and which is responsible for bioactivity. Primarily studied in relation to gallbladder contractility and pancreatic enzyme secretion, the fact that nutrients which stimulate CCK release are potent inhibitors of gastric emptying, has led to the hypothesis that CCK regulates gastric motility.

It has been known for long that infusion of pharmacological doses of CCK in huma ns delayed gastric emptying (Chey *et al*[3] 1970; Debas *et al*[5] 1975). More recently attempts have been made to mimick postprandial rises (which are, compared to the rises seen for other peptides, rather small) (Liddle *et al*[15] 1986; Kleibeuker *et al*[12] 1988).

The effect of CCK is mediated via CCK-receptors carefully characterized in the pancreas. However, CCK-receptors are present on smooth muscle cells throughout the gastrointestinal tract. In general they are distinguished into two types: CCK-A and CCK-B. The nomenclature was intended to indicate a specific localisation in either the alimentary tract (CCK-A) or the brain (CCK-B) and a distinction between peripheral and central preceptors. However this is certainly not absolute. Four classes of antagonists have been developed: Cyclic nucleotide derivatives, amino acid derivatives (example: Loxiglumide, a glutaramic acid derivative), peptide analogs and benzodiazepine derivatives (example: Devazepide formerly called L 364, 718 or MK-329).

Antagonists have been used as a tool to study the role of CCK in gastric emptying. Some animal studies showed a pronounced acceleration of gastric emptying following administration of the CCK-A antagonist L 364, 718 [Green *et al*[9] 1988]. In humans however the data are controversial. In five studies in which loxiglumide was used, three found an acceleration of gastric emptying [Fried *et al*[8] 1991; Meyer *et al*[17] 1989; Konturek *et al*[13] 1994] but the two others failed to find an effect [Corazziari *et al*[4] 1990; Niederau *et al*[19] 1990]. One study which used devazepide was also negative [Liddle *et al*[14] 1989]. These studies will not be discussed in detail, but differences in the type of meal and in the method used to study gastric emptying, may be at the basis of the controversy. It seems that the role of CCK is limited to meals which release CCK, and consequently the application of CCK-antagonists will also be limited to such meals.

Motilin was discovered as part of the studies of Brown and colleagues on the stimulatory effect of an increase in duodenal pH on motor activity in the gastric fundus and antrum. They hypothesised that this was due to the release of an hormonal substance from the duodenal mucosa, and using the motor effect on the gastric fundus as a guideline, they succeeded in isolating a 22-amino peptide from hog duodenal mucosa which they named motilin [Brown *et al*[2] 1972]. Motilin is present in endocrine cells, predominantly in the mucosa of the duodenum and the jejunum. In the fasted state it is periodically released (the stimulus for this release remains unknown) and because this release is associated with the development of phase 3 activity, it has been argued that motilin's physiological role is the initiation of phase 3 activity [Vantrappen *et al*[27] 1986]. The subject is controversial, and one argument against a causal role of motilin has been that not every phase 3 activity is accompanied by a motilin peak. However recent studies have shown that only phase 3 activity which starts in the stomach is associated with plasma motilin peaks [Bormans *et al*[1] Stolk *et al*[26] 1993]. Although motilin is probably not the only factor involved in initiating gastric phase 3 activity, it is certainly a factor which contributes to this event.

Phase 3 of the MMC is considered to be the "intestinal housekeeper" which clears the gastrointestinal lumen of meal remmants,

debris and indigestible solids. Motilin may therefore be seen as a factor contributing to the periodic gastric emptying in the fasted state. The effect of motilin on gastric emptying postprandially has been debated. Certainly, a meal suppresses rather than stimulateds motilin release, and a postprandial role of motilin seems unlikely, except perhaps in the initiation of the first phase 3 activity which marks both the end of the postprandial state and the return of the interdigestive pattern.

In 1984 Itoh *et al*[10]discovered that erythromycin mimicks the effect of motilin and induces phase 3 which starts in the stomach (and the lower esophagea l sphincter) [Itoh *et al*[10] 1984]. Later studies have shown that erythromyc in acts as a motilin agonist because it displaces motilin bound to antral smooth muscle motilin receptors and has the same regional species specificity as motilin *in vitro* [Peeters *et al*[21] 1989]. Additional arguments have further substantiated this hypothesis, which was finally proven without doubt by the discovery that Phe^3, Leu^{13} porcine motilin acts as an antagonist and blocks the contractile effects of erythromycin on the human and rabbit stomach *in vitro* [Petters *et al*[24] 1994; Depoortere *et al*[6] 1995]. Erthromycin derivatives have been developed without antibiotic properties but with enhanced potency to induce contractility. These compounds have been named motilides [Omura *et al*[20] 1987] and several are presently developed as new prokinetic drugs. Two of them EM-574 (Takeda) and ABT-229 (Abbott) appear to be in an advanced stage of development and may soon enter the clinic. All motilides are motilin agonists, and their affinity for the motilin receptor correlates with their potency *in vivo* [Peeters *et al*[23] 1994]. Their ability to accelerate gastric emptying is due to several effects on gastric motility such as: Amplification of the amplitude of antral contractions; Increased proximal gastric tone; Inhibition of pyloric pressure waves; Induction of phase 3-like patterns [Peeters *et al*[22] 1993]. Especially the last effect suggests that motilides may have a nonphysiological effect which is achieved at the expense of the sieving process accomplished by the normal fed motility pattern. In pathological conditions however this may well be the only effective way to relieve conditions of gastroparesis.

Motilides may also reduce postprandial reflex, not only as a consequence of their effect on gastric emptying, but also because there is substantial evidence that they increase LES-pressure. Certainly erythromycin has already shown to be effective in several conditions of gastroparesis such as diabetes [Dull *et al*[7] 1975, Janssens *et al*[11] 1990, Maliakkal *et al*[16] 1991, Mozwecz *et al*[18] 1990] and anorexia nervosa [Stacher *et al*[25] 1993].

For the two peptides under consideration we may therefore conclude that cholecys tokinin plays a role in postprandial emptying, while motilin plays a role in the intermittent clearing of the stomach during fasting. In both cases however these peptides are only one of several control mechanisms. Nevertheless, choosing their receptors as a therapeutic target may prove to be useful, and both CCK-antagonists and motilin agonists may be used as gastrokinetic agents. Although motilides may activate an unphysiological mechanism, they are the most promising group of substances under development at this time.

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